



شبكة المعلومات الجامعية

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ





شبكة المعلومات الجامعية



# شبكة المعلومات الجامعية

## التوثيق الالكتروني والميكرو فيلم

# جامعة عين شمس

التوثيق الالكتروني والميكرو فيلم

## قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها  
علي هذه الأفلام قد اعدت دون أية تغيرات



## يجب أن

تحفظ هذه الأفلام بعيداً عن الغبار

في درجة حرارة من 15 – 20 مئوية ورطوبة نسبية من 20-40 %

To be kept away from dust in dry cool place of  
15 – 25c and relative humidity 20-40 %



شبكة المعلومات الجامعية



# بعض الوثائق الأصلية تالفة



شبكة المعلومات الجامعية



بالرسالة صفحات  
لم ترد بالأصل

**SYNTHESIS AND SPECTRAL STUDIES  
ON HETEROCYCLIC NITROGEN  
COMPOUNDS**

**Thesis**

Submitted for the degree of (Ph.D.)

BY

**MAGDY MOHAMED HEMDAN**

(M.Sc.)

*Supervised by*

**Prof. Dr. A. F. M. Fahmy**

**Prof. Dr. N. F. Aly**

**Prof. Dr. H. A. Abd El-Hamid**

**Dr. S. A. Shiba**

Chemistry Department

Faculty of Science

Ain Shams University

Cairo

**1995**

B 4027

# SYNTHESIS AND SPECTRAL STUDIES ON HETEROCYCLIC NITROGEN COMPOUNDS

## Thesis Advisors

Prof. Dr. A. F. M. Fahmy

Prof. Dr. N. F. Aly

Prof. Dr. H. A. Abd El-Hamid

Dr. S. A. Shiba

## Approved

A. F. M. Fahmy

..... N. F. Aly ..

.. H. A. Abd El-Hamid

..... S. A. Shiba .....

Head of the Chemistry Department

A. F. M. Fahmy

Prof. Dr. A. F. M. Fahmy

## ACKNOWLEDGMENT

*The author wishes to express his deep thanks and gratitude to Prof. Dr. A.F. Fahmy, head of chemistry department and Professor of organic chemistry, chemistry department, Faculty of Science, Ain Shams University, for suggesting the problem, valuable discussion and criticism.*

*He also wishes to express his gratitude to prof. Dr. Hoda Abdel-Hamid, Prof. of organic chemistry, Ain Shams University, for her encouragement, valuable help and criticism during the progress of the work.*

*Thanks to Prof. Dr. Nawal.F. Aly, Professor of organic chemistry, and Dr. S.A. Shiba Assistant professor of organic chemistry, chemistry Department, Faculty of Science, Ain Shams University, for there supervision and encouragement.*

M. Hemdan



# CONTENTS

	page
<b>SUMMARY</b>	i
<b>INTRODUCTION</b>	1
<b>SOME BASIC CONSIDERATIONS</b>	1
<b>SYNTHESIS OF ISOTHIOCYANATES</b>	5
(1) Synthesis of Alkyl and Aryl Isothiocyanates	5
(2) Synthesis of 1-Alkenyl Isothiocyanates	31
(3) Synthesis of Acyl Isothiocyanates	34
(4) Synthesis of Thiocyl Isothiocyanates	36
(5) Synthesis of Imino alkyl Isothiocyanates	37
(6) Synthesis of Amino Isothiocyanates	37
(7) Synthesis of Sulfonyl Isothiocyanates	38
(8) Synthesis of Phosphoryl Isothiocyanates	38
(9) Synthesis of Silyl Isothiocyanates	39
<b>ISOTHIOCYANATES IN HETEROCYCLIC SYNTHESIS</b>	40
(1) Synthesis Of Four-Membered Heterocycles	40
(2) Synthesis of Five-Membered Heterocycles	40
(3) Synthesis of Six-Membered Heterocycles	57
(4) Synthesis of Seven-Membered Heterocycles	64
(5) Synthesis of Benzo Heterocycles	65
(6) Synthesis of Non-Benzo Heterocycles	68
(7) Synthesis of Polycyclic Heterocycles	71
(8) Conclusion	73
<b>DISCUSSION</b>	
<b>Part I</b>	74
<b>Chapter I</b>	
The Use of p-N-Succinimidobenzoyl Isothiocyanate in Heterocyclic Synthesis	74
I. Synthesis of p-N-Succinimidobenzoyl Isothiocyanate	76
II. The Use of Isothiocyanate in Heterocyclic Synthesis	77
(1) Synthesis of 2-phenyl-1-H-(p-N-Succinimidophenyl)- $\Delta^3$ -1,2,4-triazoline-5-thione	77
(2) Synthesis of 3-Aryl-4-(p-N-Succinimidobenzoyl)- $\Delta^2$ -1,2,4-triazoline-5-thione	80

(3) Synthesis of 3-(p-N-Succinimidobenzoyl)-1,3-quinazolin-4-one-2-thione	86
(4) Synthesis of 2-(p-N-Succinimidobenzamid)-2-thiol-1,3-oxazolidine-5-one	89
(5) Synthesis of 3-(p-N-Succinimidobenzoyl)-1,3-thiazolidine-5-one-2-thione	91
(6) Synthesis of 2-N-(p-N-Succinimidobenzamid)-1,3-benzoxazole	94
(7) Synthesis of 2-(p-N-Succinimidophenyl)-5-carboxamido-6-isopropylidene amino-4-H-1,3-oxazine-4-thione	95
(8) Synthesis of 6-Amino-4-(p-N-Succinimidophenyl)-1,3,5-triazin-2-thion and 6-Isopropylidene amino-2-(p-N-succinimidophenyl)-1,3,5-oxadiazin-4-thione	97
III. Synthesis of N-Aryl-N'-p-N-succinimidophenyl Thiourea	99
IV. Synthesis of Ethyl-N-(succinimidobenzoyl) thiocarbamate	101
<b>Chapter II</b>	
Electron Impact Mass Spectral Study	104
<b>PART II.</b>	
The use of $\alpha$ -Cyano- $\beta$ -phenylcinnamoyl Isothiocyanate in Heterocyclic Synthesis	131
(1) Synthesis of $\alpha$ -Cyano- $\beta$ -phenylcinnamoyl Isothiocyanate	131
* Synthesis of 5-Cyano-6,6-diphenyl-oxazine-4-one-2-thione	132
(2) Synthesis of 1-(N-benzamido)-5-cyano-6,6-diphenyl-pyrimidine-4-one-2-thione	137
(3) Synthesis of 1-Aryl-5-cyano-6,6-diphenyl-hexahydro-pyrimidine-4-one-2-thione	140
(4) Synthesis of Quinazoline derivative	144
<b>FIGURES</b>	
<b>EXPPERIMENTAL</b>	152
<b>REFERENCES</b>	168

# SUMMARY

## Summary

Heterocyclic rings, like triazolines, quinazolines, oxazolidines, thiazoles, benzoxazoles, oxazines and oxadiazines are reported to exhibit biological activity. The aim of this work was:

(1) The use of p-N-succinimidobenzoyl isothiocyanate to prepare these heterocycles substituted with pyrrolidine dione hopping to enhance their biological activity.

(ii) The use of  $\alpha$ -cyano- $\beta$ -phenylcinnamoyl isothiocyanate as a start for the synthesis of oxazine, pyrimidine as well as quinazoline system. All these systems are substituted with a cyano group and this is expected to increase their biological activity.

## Part I

p-N-succinimidobenzoyl isothiocyanate (I) was prepared from its acid chloride by treating its solution in acetone with ammonium thiocyanate. The isothiocyanate obtained *in situ* was used in heterocyclic synthesis.

Treatment of (I) with phenyl hydrazine afforded 2-phenyl-1-H-3-(p-N-succinimidophenyl)- $\Delta^3$ -1,2,4-triazoline-5-thione (V).

Reaction with aroyl hydrazine e.g. benzoylhydrazine and p-chlorobenzoyl hydrazine gave thiosemicarbazide derivatives (VIIa-b), which have been used as precursors to synthesize 3-aryl-4-(p-N-succinimidobenzoyl)- $\Delta^2$ -1,2,4-triazoline-thiones (VIIIa,b) by cyclization using polyphosphoric acid.

When isothiocyanate (I) was treated with anthranilic acid, the diaryl thiourea derivative (IX) was obtained, the latter was converted to 3-(p-N-succinimidobenzoyl)-1,3-quinazolin-4-one-2-thione (X) by refluxing in acetic anhydride.

Reaction of (I) with glycine produced an equilibrium mixture of the diaryl thiourea (XI) and 2-(p-N-succinimidobenzamide)-2-thiol-1,3-oxazolidine-5-one (XII).

Treatment of (I) with thioglycollic acid, followed by heating with acetic anhydride produced 3-(p-N-succinimidobenzoyl)-1,3-thiazolidine-5-one-2-thione (XIV).

Thiocarbamate derivative (XV), produced from the reaction of o-aminophenol with isothiocyanate (I) was converted upon fusion to 2-N-(p-N-succinimidobenzamide)-1,3-benzoxazole (XVI).

Cyanoacetamide condenses with isothiocyanate (I), leading to the formation of 2-(p-N-succinimidophenyl)-5-carboxamido-6-isopropylidenamino-4-H-1,3-oxazin-4-thione (XVIII).

Finally, guanidine reacts with isothiocyanate (I) producing a mixture of 6-amino-4-(p-N-succinimidophenyl)-1,3,5-triazin-2-thione (XIX) and 6-isopropylidinamino-2-(p-N-succinimidophenyl)-1,3,5-oxadiazin-4-thione (XX).

In addition to the above mentioned heterocycles our interest to synthesise biologically active compounds was extended to the synthesis of thiourea derivatives (XXIa-c) through the reaction of isothiocyanate (I)

with aromatic amines, as well as the synthesis of thiocarbamates (XXII) by reaction of (I) with ethanol.

All the above mentioned compounds were proved by extensive spectral studies using I.R,  $^1\text{H}$ . NMR as well as a detailed study of their mass spectra.

## Part II

$\alpha$ -cyano- $\beta$ -phenylcinnamoyl isothiocyanate (XXV) was prepared from  $\alpha$ -cyano- $\beta$ -phenylcinnamoylchloride by treatment with ammonium thiocyanate. When treated with water, 5-cyano-6,6-diphenyl-oxazin-4-one-2-thione (XXVI) was produced.

Reaction of (XXV) with benzoylhydrazine produces 1-(N-benzamido)- 5- cyano-6,6-diphenyl-pyrimidin-4-one-2-thione (XXVIII).

The synthesis of 1-aryl-5-cyano-6,6-diphenyl-hexahydro-pyrimidin-4-one-2-thione (XXXa-c), was through the reaction of isothiocyanate (XXV) with aromatic amines.

Reaction of (XXV) with anthranilic acid yields the diaryl thiourea (XXXIII) used as a precursor in the synthesis of-3-[ $\alpha$ -cyano- $\beta$ -phenylcinnamoyl]quinazolin-4-one-2-thione (XXXV) or quinazolin-4-one-2-thione (XXXIV) by treatment of (XXXIII) with acetic anhydride for different reaction periods.

The structure of all the prepared compounds was proved by elemental analysis, I.R,  $^1\text{H}$ . NMR and mass spectra.



# INTRODUCTION